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Disclaimer

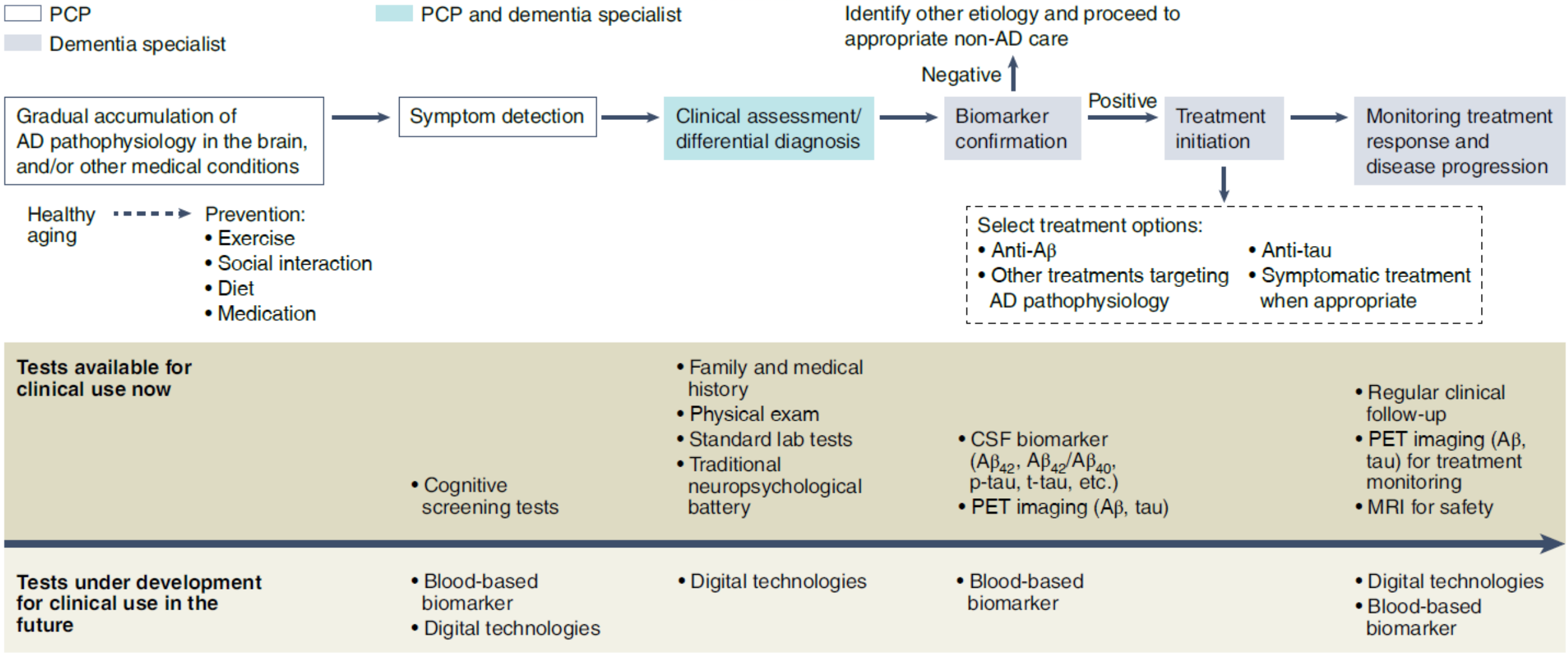
- I have received funding for research through my institution from
  - The National Research Council of Singapore
  - Eisai
  - Roche
  - BMS

- I have served in an advisory capacity to
  - Eisai
  - Lilly
  - Actinogen
  - Cerecin
  - BMS

PERSPECTIVE
https://doi.org/10.1038/s43587-022-00269-x
nature aging

Designing the next-generation clinical care pathway for Alzheimer's disease

Harald Hampel[1]✉, Rhoda Au[2], Soeren Mattke[3], Wiesje M. van der Flier[4], Paul Aisen[5], Liana Apostolova[6], Christopher Chen[7], Min Cho[1], Susan De Santi[1], Peng Gao[1], Atsushi Iwata[8], Ricky Kurzman[1], Andrew J. Saykin[9], Stefan Teipel[10,11], Bruno Vellas[12], Andrea Vergallo[1], Huali Wang[13] and Jeffrey Cummings[14]



- **Current Implementation Barriers- test availability and accessibility**
- APAC-Specific Considerations- AD+CVD co-pathology: Impact on biomarker interpretation; Ethnic differences in biomarker cut-offs
- Future outlook: biomarkers in the pipeline, preclinical screening,

Emerging Techniques for Blood-Based Measurement of Amyloid Beta

Review

Blood-based high sensitivity measurements of beta-amyloid and phosphorylated tau as biomarkers of Alzheimer's disease: a focused review on recent advances

Joyce R. Chong,[1,2] Nicholas J. Ashton,[3,4,5,6] Thomas K. Karikari,[6,7] Tomotaka Tanaka,[1,8,9] Michael Schöll,[3,6,10] Henrik Zetterberg ,[6,10,11,12] Kaj Blennow,[6,12] Christopher P. Chen,[1,2] Mitchell K.P. Lai [1,2]

- Immunoprecipitation-Mass Spectrometry (IP-MS)
- Single Molecule Array (SIMOA) immunoassay
- Amplified Plasmonic Exosome (APEX) platform
- Immunomagnetic Reduction (IMR)
- Interdigitated microelectrode system
- Elecsys immunoassays (Roche)
- Meso Scale Discovery platform

J Neurol Neurosurg Psychiatry 2021

Improved sensitivity compared with conventional assays

and/or

measuring specific isoforms of Aβ species that may be more relevant to AD pathology

nature reviews neurology https://doi.org/10.1038/s41582-024-00977-5

Consensus statement

Check for updates

Acceptable performance of blood biomarker tests of amyloid pathology – recommendations from the Global CEO Initiative on Alzheimer's Disease

Anti-amyloid treatments for early symptomatic Alzheimer disease have recently become clinically available in some countries, which has greatly increased the need for biomarker confirmation of amyloid pathology. Blood biomarker (BBM) tests for amyloid pathology are more acceptable, accessible and scalable than amyloid PET or cerebrospinal fluid (CSF) tests, but have highly variable levels of performance. The Global CEO Initiative on Alzheimer's Disease convened a BBM Workgroup to consider the minimum acceptable performance of BBM tests for clinical use. Amyloid PET status was the reference standard.

For use as a triaging test before subsequent confirmatory tests such as amyloid PET or CSF tests, the BBM Workgroup recommends that a BBM test has a sensitivity of ≥90% with a specificity of ≥85% in primary care and ≥75–85% in secondary care depending on the availability of follow-up testing.

For use as a confirmatory test without follow-up tests, a BBM test should have performance equivalent to that of CSF tests — a sensitivity and specificity of ~90%.

Importantly, the predictive values of all biomarker tests vary according to the pre-test probability of amyloid pathology and must be interpreted in the complete clinical context. Use of BBM tests that meet these performance standards could enable more people to receive an accurate and timely Alzheimer disease diagnosis and potentially benefit from new treatments.

Plasma P-tau181 to Aβ42 ratio is associated with brain amyloid burden and hippocampal atrophy in an Asian cohort of Alzheimer's disease patients with concomitant cerebrovascular disease

Alzheimer's Dement. 2021;1–14.

Joyce R. Chong[1,2] | Nicholas J. Ashton[3,4,5,6] | Thomas K. Karikari[3] | Tomotaka Tanaka[2,7,8] | Francis N. Saridin[1,2] | Anthonin Reilhac[8] | Edward G. Robins[8,9] | Ying-Hwey Nai[8] | Henri Vrooman[10] | Saima Hilal[1,2,11] | Henrik Zetterberg[3,12,13,14] | Kaj Blennow[3,12] | Mitchell K.P. Lai[1,2] | Christopher P. Chen[1,2]

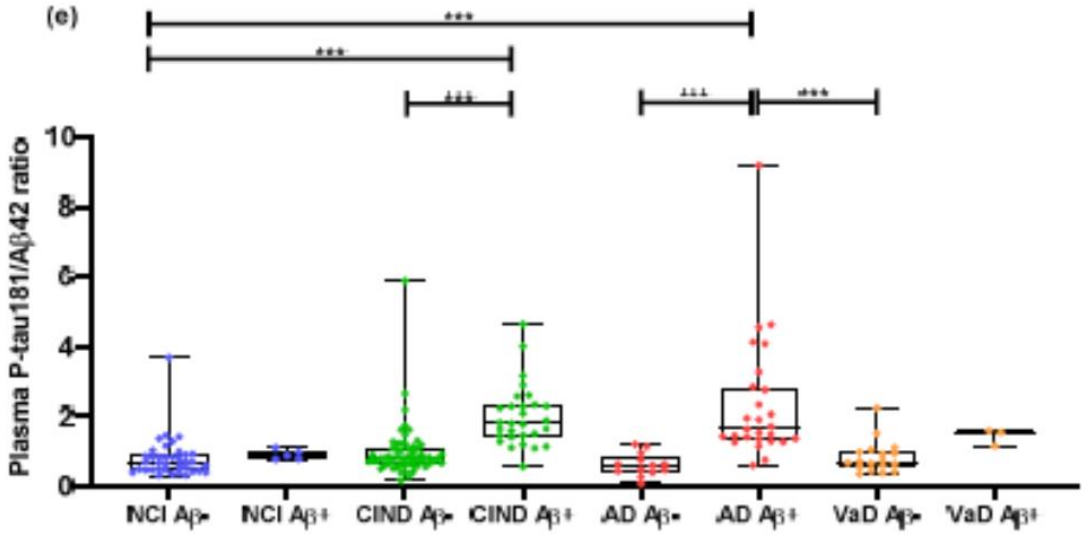
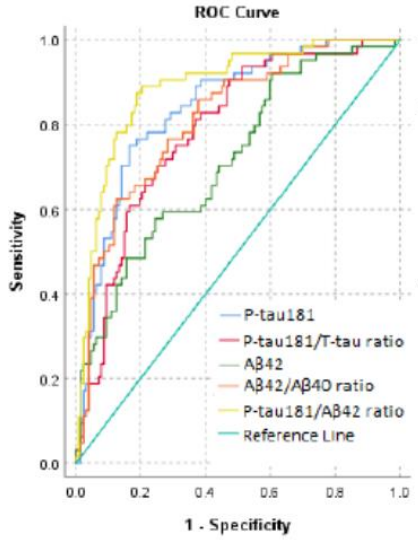
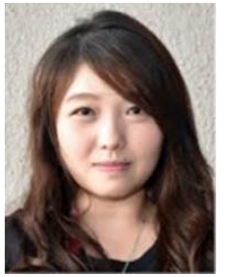


Figure 2. ROC analysis for distinguishing PET Aβ+ and Aβ- subjects

(a) All subjects (n=191)



Plasma Biomarkers	AUC	P-value (compared with P-tau181/Aβ42 ratio)	(95% CI)	Sensitivity	Specificity
P-tau181/Aβ42 ratio	0.889	NA	(0.840, 0.938)	87.5%	81.1%
P-tau181	0.840	0.021	(0.782, 0.898)	75.0%	83.5%
Aβ42/Aβ40 ratio	0.814	0.041	(0.751, 0.877)	62.5%	87.4%
P-tau181/T-tau ratio	0.786	0.001	(0.720, 0.853)	70.3%	74.8%
Aβ42	0.715	<0.001	(0.638, 0.791)	57.8%	75.6%



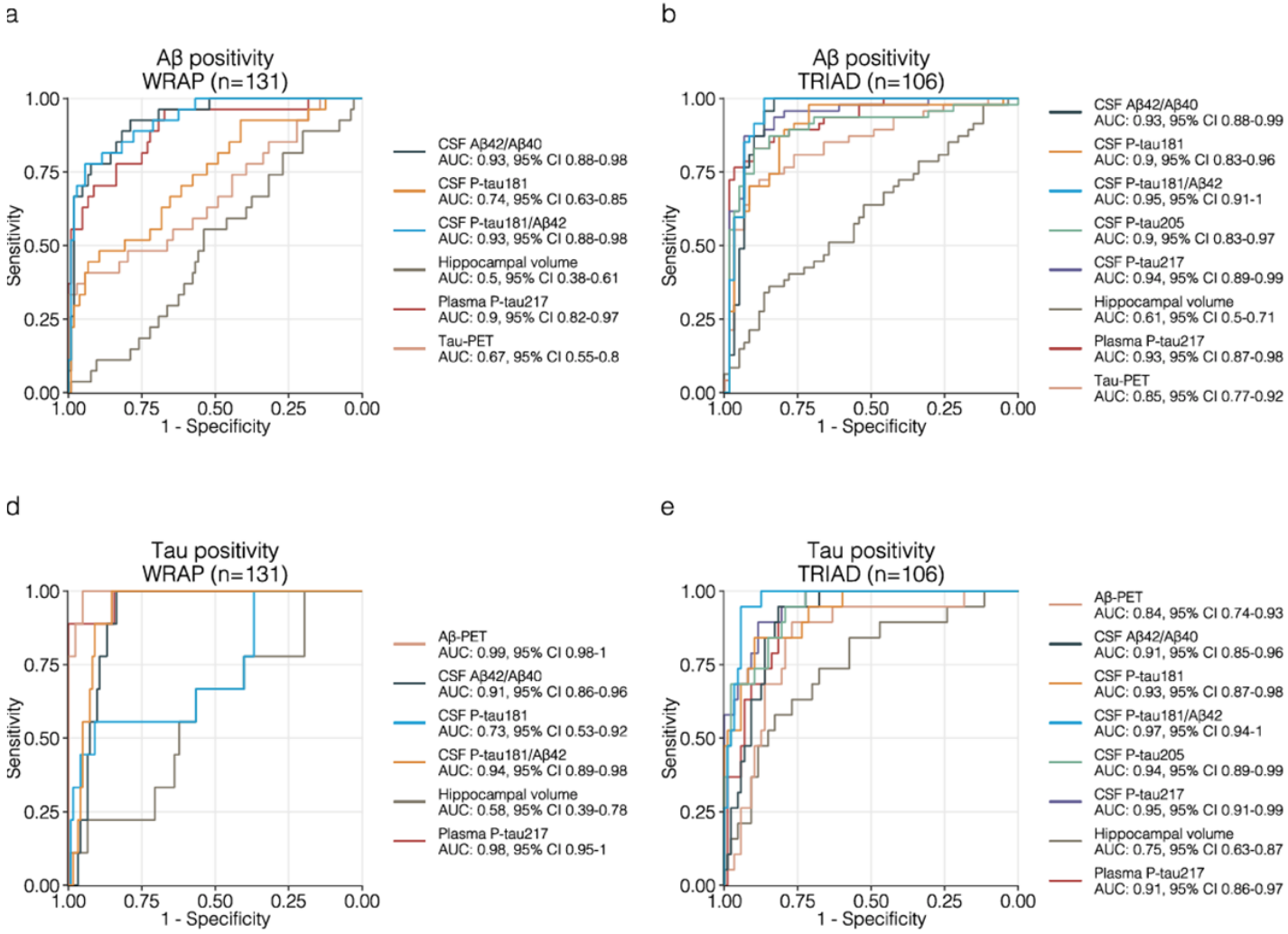
ALZpath P-tau217

JAMA Neurol. 2024;81(3):255-263. doi:10.1001/jamaneurol.2023.5319
Published online January 22, 2024.

JAMA Neurology | Original Investigation

Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology

Nicholas J. Ashton, PhD; Wagner S. Brum; Guglielmo Di Molfetta, MSc; Andrea L. Benedet, PhD; Burak Arslan, MD; Erin Jonaitis, PhD; Rebecca E. Langhough, PhD; Karly Cody, PhD; Rachael Wilson, PhD; Cynthia M. Carlsson, PhD; Eugeen Vanmechelen, PhD; Laia Montoliu-Gaya, PhD; Juan Lantero-Rodriguez, PhD; Nesrine Rahmouni, MSc; Cecile Tissot, PhD; Jenna Stevenson, PhD; Stijn Servaes, PhD; Joseph Therriault, PhD; Tharick Pascoal, MD, PhD; Alberto Lleó, MD, PhD; Daniel Alcolea, MD, PhD; Juan Fortea, MD, PhD; Pedro Rosa-Neto, MD, PhD; Sterling Johnson, MD, PhD; Andreas Jeromin, PhD; Kaj Blennow, MD, PhD; Henrik Zetterberg, MD, PhD



- **Plasma P-tau217 showed comparable performance with other established CSF biomarkers in detecting abnormal amyloid PET and tau PET**

Medical News

What to Know About the First FDA-Cleared Blood Test for Alzheimer Biomarkers

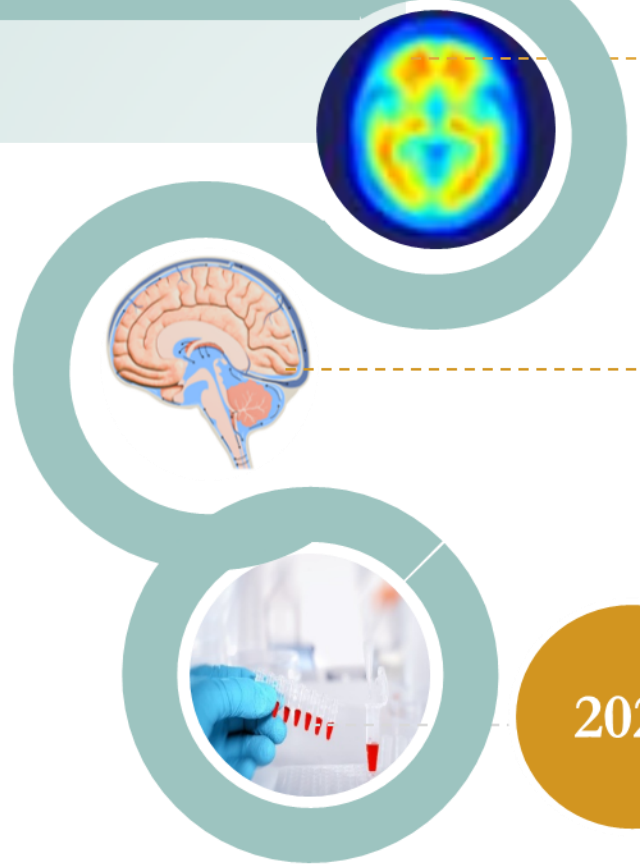
JAMA July 15, 2025 Volume 334, Number 3

Rita Rubin, MA

Fujirebio Diagnostics

Lumipulse p-tau 217 / aß 42 ratio approved by FDA on May 16th 2025

Biomarkers of AD-Related Pathological Changes Can Facilitate an Early Diagnosis



Amyloid PET imaging

Three amyloid PET tracers are available for use in patients being evaluated for AD and other causes of cognitive decline[1–3]

Lumipulse G CSF β-amyloid Aβ42/40 ratio

First FDA-approved CSF assay to receive IVD clearance; assay measures **CSF Aβ42/40 ratio**[4]

Elecsys p-tau181/Aβ42 or t-tau/Aβ42 ratios

IVD clearance was received for 2 additional CSF assays, which measure **CSF p-tau181/Aβ42** and **t-tau/Aβ42 ratio**[5,6]

2025

Lumipulse G p-tau217/Aβ42 plasma ratio assay

First FDA-cleared blood test for AD diagnosis. Assay measures **p-tau217/Aβ42 ratio** in adults aged ≥55 years with cognitive symptoms[7]

Elecsys® p-tau181

FDA-cleared blood test for AD diagnosis. Assay measures **p-tau 181** in adults aged ≥55 years with cognitive symptoms in a primary care setting[8]

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDA, US Food and Drug Administration; IVD, in vitro diagnostic; p-tau, phosphorylated tau; PET, positron emission tomography; t-tau, total tau.

1. Vizamyl™ Prescribing Information. https://www.gehealthcare.com/-/jssmedia/widen/2018/01/25/0204/gehealthcarecom/migrated/2018/02/19/0834/er-clinical-product-info-vizamyl-203-8c17d992a0aa9aadb2e446d7f5580a8b_43-1067c_vizamyl_pdf.pdf (Accessed August 2025); 2. Neuraceq™ Prescribing Information. https://neuraceq.com/wp-content/uploads/PRESCRIBING-INFORMATION.pdf (Accessed August 2025); 3. Amyvid™ Prescribing Information. https://pi.lilly.com/us/amyvid-uspi.pdf (Accessed August 2025); 4. FDA DEN200072. https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN200072.pdf (Accessed August 2025); 5. FDA K221842. https://www.accessdata.fda.gov/cdrh_docs/pdf22/K221842.pdf (Accessed August 2025); 6. FDA K231348. https://www.accessdata.fda.gov/cdrh_docs/reviews/K231348.pdf (Accessed August 2025); 7. US Food and Drug Administration. FDA News Release - FDA Clears First Blood Test Used in Diagnosing Alzheimer's Disease. https://www.fda.gov/news-events/press-announcements/fda-clears-first-blood-test-used-diagnosing-alzheimers-disease (Accessed August 2025); 8https://diagnostics.roche.com/global/en/products/lab/elecsys-phospho-tau-181p-plasma-pid00001042.html).

- Current Implementation Barriers- test availability and accessibility
- **APAC-Specific Considerations- AD+CVD co-pathology: Impact on biomarker interpretation; Ethnic differences in biomarker cut-offs**
- Future outlook: biomarkers in the pipeline, preclinical screening,

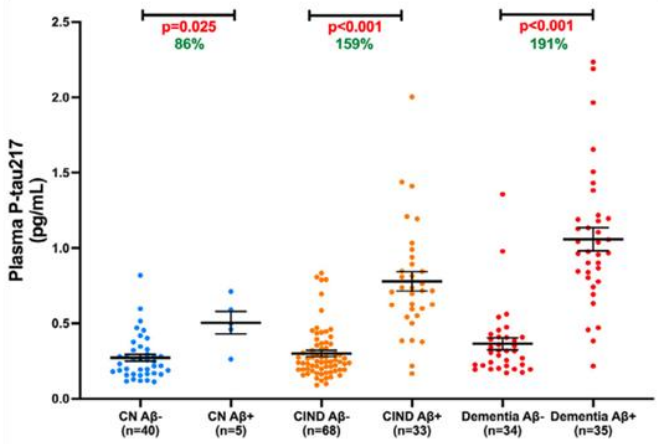
DOI: 10.1002/alz.14502

RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Clinical utility of plasma p-tau217 in identifying abnormal brain amyloid burden in an Asian cohort with high prevalence of concomitant cerebrovascular disease

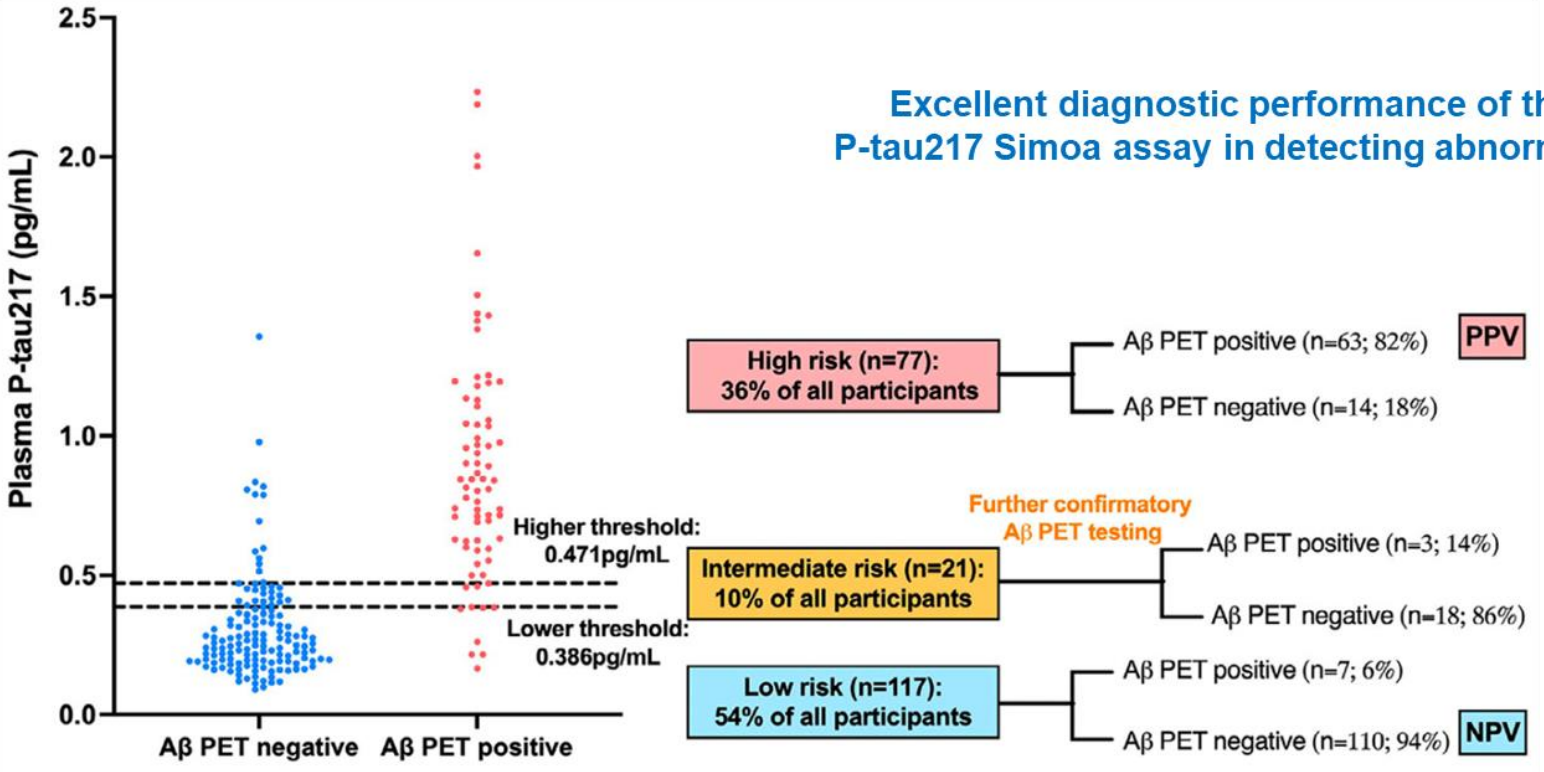
Joyce R. Chong[1,2] | Saima Hilal[1,2,3] | Boon Yeow Tan[4] | Narayanaswamy Venketasubramanian[5] | Michael Schöll[6,7,8] | Henrik Zetterberg[6,7,9,10,11,12] | Kaj Blennow[6,9,13,14] | Nicholas J. Ashton[6,15] | Christopher P. Chen[1,2] | Mitchell K. P. Lai[1,2]



(A) **All participants (142 Aβ- vs 73 Aβ+)**

	AUC	95% CI	p-value
Basic clinical measures (Age, sex, MMSE)	0.760	0.693-0.827	
Full diagnostic workup (Basic clinical measures + clinical diagnosis + MTA scores + APOE ε4 status)	0.819	0.760-0.879	0.026#
Plasma P-tau217 only	0.923	0.882-0.965	<0.001# 0.003*
Basic clinical measures + plasma P-tau217	0.937	0.904-0.970	<0.001# <0.001* 0.23†
Full diagnostic workup + plasma P-tau217	0.953	0.928-0.979	<0.001# <0.001* 0.023† 0.061^

Excellent diagnostic performance of the commercial plasma P-tau217 Simoa assay in detecting abnormal brain amyloid burden



A 3-range strategy consisting of a higher cut-off to rule in AD (90% specificity; high risk group for amyloid PET positivity [Aβ+]) and a lower cut-off to rule out AD (90% sensitivity; low risk group for PET Aβ+) were defined.

Chong et al. 2025, Alzheimers Dement

Received: 30 October 2024 | Revised: 27 December 2024 | Accepted: 28 December 2024

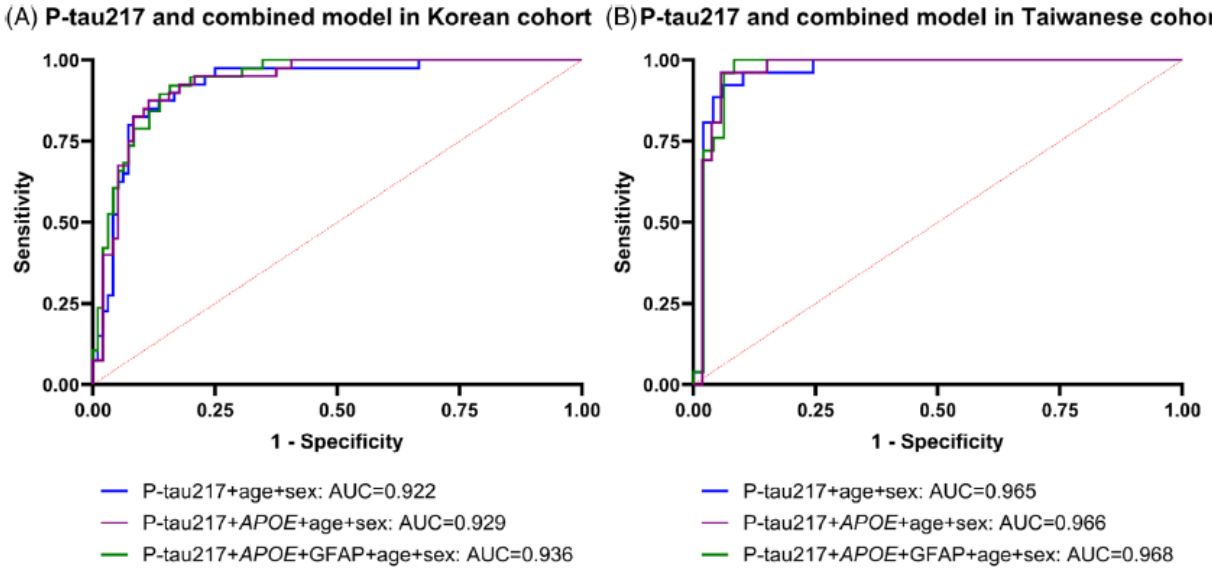
DOI: 10.1002/alz.14565

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Cross-cultural validation of plasma p-tau217 and p-tau181 as precision biomarkers for amyloid PET positivity: An East Asian study in Taiwan and Korea

Yung-Shuan Lin[1,2,3] | Hyuk Sung Kwon[4] | Wei-Ju Lee[3,5,6] | Mina Hwang[4] | Jee Hyang Jeong[7] | Seong-Ho Koh[4] | Seong Hye Choi[8] | Jong-Ling Fuh[1,2,3]



(C)

	AUC (Confidence interval)
Establishing the predicting model from Taiwanese cohort	
Three-biomarker model: Plasma p-tau217, *APOE*, GFAP	0.968 (0.926–1.000)
Two-biomarker model: Plasma p-tau217, *APOE*	0.966 (0.923–1.000)
Cross-validating the same model in Korean cohort	
Three-biomarker model: Plasma p-tau217, *APOE*, GFAP	0.923 (0.880–0.967)
Two-biomarker model: Plasma p-tau217, *APOE*	0.929 (0.888–0.971)

	AUC (Confidence interval)
Establishing the predicting model from Korean cohort	
Three-biomarker model: Plasma p-tau217, *APOE*, GFAP	0.936 (0.895–0.976)
Two-biomarker model: Plasma p-tau217, *APOE*	0.929 (0.886–0.973)
Cross-validating the same model in Taiwanese cohort	
Three-biomarker model: Plasma p-tau217, *APOE*, GFAP	0.967 (0.923–1.000)
Two-biomarker model: Plasma p-tau217, *APOE*	0.956 (0.906–1.000)

- Current Implementation Barriers- test availability and accessibility
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- **Future outlook: biomarkers in the pipeline, preclinical screening,**

Medical News

What to Know About the First FDA-Cleared Blood Test for Alzheimer Biomarkers

JAMA July 15, 2025 Volume 334, Number 3

Rita Rubin, MA

Fujirebio Diagnostics

Other Blood Tests are also seeking FDA approval

Beckmann Coulter
Roche ptau217
C2N
Quanterix

Many more available and marketed

Received: 18 June 2025 | Revised: 11 July 2025 | Accepted: 14 July 2025

DOI: 10.1002/alz.70535

GUIDELINES

Alzheimer's & Dementia®
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Alzheimer's Association Clinical Practice Guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings

TABLE 2 Recommendations and remarks for the use of BBM tests in patients with objective cognitive impairment presenting for specialized care

Clinical question	Recommendation
Should a BBM test be incorporated as a ***triaging*** **test**[a] to determine the presence or absence of AD pathology in the diagnostic workup of individuals with cognitive impairment (including those with MCI or dementia) presenting for specialized care for memory disorders?	In patients with objective cognitive impairment presenting for specialized memory-care, the panel suggests *using a* ***high-sensitivity BBM test***[b] as a triaging test in the diagnostic workup of AD. (Conditional recommendation, Low certainty evidence[c])
[a]*A triaging test refers to a test in which a negative result rules out AD pathology with high probability, whereas a positive result should be confirmed using another method, such as CSF AD biomarkers or amyloid PET.*	[b]*The panel defined acceptable diagnostic test accuracy for triaging to be at least 90% sensitivity and 75% specificity for a reference test (CSF AD biomarkers, amyloid PET, or AD neuropathology). A systematic review of relevant studies can be found here.* https://app.magicapp.org/#/guideline/nyO1Yj. *Information will be updated based on future systematic reviews.* [c]*Certainty of the evidence is based on tests meeting acceptable diagnostic test accuracy.*
Should a BBM test serve as a substitute for CSF analysis or amyloid PET as a ***confirmatory*** **test**[d] to determine the presence or absence of AD pathology in the diagnostic workup of patients with cognitive impairment (MCI or dementia) presenting for specialized care for memory disorders?	In patients with objective cognitive impairment presenting for specialized memory-care, the panel suggests using a ***high-sensitivity and high-specificity***[e] BBM test as a confirmatory test in the diagnostic workup of AD (conditional recommendation, Low certainty evidence[f]).
[d]*A confirmatory test refers to a test in which a negative test rules out AD pathology, and a positive test confirms AD pathology with a high probability.*	[e]*The panel defined acceptable diagnostic test accuracy for confirmatory testing to be at least 90% sensitivity and 90% specificity for a reference test (CSF AD biomarkers, amyloid PET, or AD neuropathology). A systematic review of relevant studies can be found here.* https://app.magicapp.org/#/guideline/nyO1Yj. *Information will be updated based on future systematic reviews.* [f]*Certainty of the evidence is based on tests meeting acceptable diagnostic test accuracy.*

Good practice statement

A BBM test should not be obtained before a comprehensive clinical evaluation by a healthcare professional, and test results should always be interpreted within the clinical context. The panel urges clinicians to consider the pretest probability of AD pathology for each patient when deciding whether or not to use a BBM test.

In the following clinical scenarios, a BBM test may not be appropriate:

1. When there is low utility in knowing whether AD pathology is present..
2. Patients with obvious modifiable or temporary conditions that account for cognitive impairment.
3. Patients with limited life expectancy
4. Patients with a history of conditions that can affect the brain and that may impact levels of a given BBM
5. Patients with medical conditions that may affect the levels of a given BBM
6. Patients taking medications that may impact levels of a given BBM

Clinical Use of Alzheimer Disease Biomarkers: Ethical and Social Considerations

- "Benefit" involves optimizing health outcomes for individual patients and is a threshold factor in establishing whether clinical adoption of AD biomarker testing is ethically justified
- Disease-modifying therapy is only indicated for individuals with mild cognitive impairment or mild dementia with evidence of amyloid on PET or CSF. **Hence biomarker testing should be performed if the results affect clinical management.**
- However, restricting "benefit" to therapeutic benefit would limit biomarker testing to people who meet these criteria and do not have exclusion criteria (eg, comorbid cardiovascular diseases) and would exclude people who may otherwise **benefit from testing for nontherapeutic reasons, including to establish certainty regarding diagnosis and future planning purposes.**

Clinical Use of Alzheimer Disease Biomarkers: Ethical and Social Considerations

- Restricting access to biomarker testing on the basis of therapeutic benefit could **preclude individuals from accessing other services that are often available through specialty centers** (eg, increased monitoring, social work services, genetic testing and counseling)
- People may seek out biomarker testing before symptoms emerge, particularly if they carry a **known genetic marker for AD or have a strong family history.**
- If benefit is reframed to consider personal use or nontherapeutic clinical decision making, there could be justifications that support asymptomatic biomarker testing. **However, the potential consequences are more substantial.**

Clinical Use of Alzheimer Disease Biomarkers: Ethical and Social Considerations

- Biomarker testing is most ethically supportable for tests that produce the highest degree of accuracy with the least invasiveness and lowest risk or burden.

- **Clinical adoption requires a full understanding of test accuracy.** People should be informed of **false positives** which could lead to inappropriate therapeutic decisions and patient distress as well as **false negatives** which could result in increased diagnostic testing, false assurance, and missed timely treatment opportunities.

- Challenges associated with test accuracy include
  - interassay variability, lack of standardized cutoff points hinder evaluation of test performance.
  - **individual comorbidities** (eg, renal impairment, obesity, cardiovascular disease).
  - racial and ethnic differences

Clinical Use of Alzheimer Disease Biomarkers: Ethical and Social Considerations

- Research results on disclosure outcomes (distress) of genetic and biomarker status may vary depending on individual-level characteristics (eg, asymptomatic vs symptomatic, known family risk). **How clinical disclosure will diverge is unknown**.

- Distress may also be accompanied by stigma and the risk of discrimination. **AD biomarker testing advancement may shift this stigma, particularly for those who are asymptomatic or early in the disease process and now carry labels associated with being at risk and confirmed to have AD pathology.**

- Third parties may be able to access health information legally in limited circumstances. For example, insurers or employers can learn of an individual's biomarker status which could result in discrimination. **Documentation of AD biomarker status in the medical record may increase risks of discrimination.**

Clinical Use of Alzheimer Disease Biomarkers: Ethical and Social Considerations

- BBBs may increase accessibility by the scalability of biomarker testing. However, although use of BBBs removes the need for specialized technical equipment (eg, PET scanners), **scalability may be limited by health care capacity to offer and disclose test results, storage facilities, and access to laboratories equipped to analyze results.**
- Previous research has demonstrated that gerontologists feel unprepared to counsel people on genetic testing results or to help interpret direct-to-consumer test results. Primary care clinicians and other nondementia specialists may report similar limitations regarding biomarker testing.
- **Research is needed to understand whether primary care and nondementia specialty centers are prepared to offer biomarker testing—specifically BBB testing—as part of regular practice.**

Precision Medicine for AD has arrived!

Detecting and intervening in early dementia is important

Blood biomarkers hold great promise but challenges include real world validation and interpretation

Disease modifying treatments are now available for early AD and more such treatments are being developed

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